concerned are confident to trust, partly because the absence of bureaucratic control has enabled advice and decisions to be given quickly, and, if necessary, informally. Why then does the Government now consider that statutory backing "would give greater reassurance and should not be further delayed"? One reason advanced is that the Dunlop Committee itself has said it believed "the arrangements ought to be given permanence within the framework of legislation."[3] But it seems very questionable whether the Committee, in suggesting further statutory backing, had in mind anything like the all-pervasive Governmental control now proposed. A second reason for introducing the new legislation is that it is "believed to be broadly compatible with the arrangements" that will be laid down for the European Economic Community under the Treaty of Rome—that is, the Common Market. But, since other arrangements might be equally compatible, the ones set out in the White Paper should not be regarded as the last word in that respect.

That thorough checks on the manufacture and marketing of drugs are needed must be beyond dispute. At present they are satisfactorily exercised by the pharmaceutical industry in the course of research and manufacture, by the Dunlop Committee, and by the doctors who test and prescribe drugs. Despite the White Paper's expressed intention "to retain the flexible administration that has been so effective under the voluntary scheme," the ability of this or any Government to carry it out must arouse misgivings. Bureaucratic control rarely allows flexible administration. Nor is it clear how a system that vests in a Minister, a member of a political party, such complete control over the development and supply of drugs can command the confidence that the Dunlop Committee enjoys.

Some indication, perhaps no more, of the way the wind is blowing may be noted in the White Paper's remarks on the *British Pharmacopoeia*—to be taken over from the G.M.C. by the proposed Medicines Commission. "It is not intended," says the White Paper, "to prohibit the publication by other bodies of similar compendia . . . but as the scope of the compendia prepared under the aegis of the Commission widens, the scope of other compendia might diminish." The difficulty is to prevent much more than the scope of "compendia" from diminishing when control becomes centralized in Whitehall. The great danger is a deadening of the impulse to research that has revolutionized therapeutics in the last 30 years.

[1] *Brit. med. J.*, 1967, **3**, 688.
[2] *Forthcoming Legislation on the Safety, Quality and Description of Drugs and Medicines.* Cmnd. 3395. 1967. H.M.S.O.
[3] Committee on Safety of Drugs, *Report for the Year Ended 31 December 1965.* 1966. H.M.S.O.

Poisoning from Paraquat

The question of differentiating "toxicity" from "hazard" is no more clearly illustrated than in the case of the herbicide paraquat (1,1′ dimethyl-4,4′-dipyridilium). In Great Britain there has been no death among people occupationally exposed to pesticides since 1953, and in each year fewer than 20 cases of poisoning are reported to the Ministry of Agriculture by their vigilant inspectors. These reported cases are mostly trivial—rashes or the effects of splashes in the eye—with one or two cases of systemic poisoning.[1]

The dipyridilium herbicides are a British invention, which could in some circumstances revolutionize agriculture by removing the need for the plough. The herbicides of this group act immediately on plants and are inactivated on coming into contact with soil. They are widely used for general control of weeds among plantation crops in Britain and overseas, and also for defoliation to facilitate harvesting of crops like cotton and potatoes. Workers applying these substances have sometimes suffered some nose bleeding owing to inhalation of spray droplets, but nothing more serious. The extraordinary activity of these compounds as weedkillers has led on several occasions to the illicit removal of concentrates from bulk and their diversion to private hands in small containers. When the container was a beer bottle two casualties resulted,[2] and other similar cases have been reported to the manufacturer.

At page 721 of the *B.M.J.* this week Drs. Ch. Almog and E. Tal record an unusual case of suicide by the subcutaneous injection of a 20% solution of paraquat. Animal experiments indicate that once absorbed into the body above a certain dose paraquat induces an irreversible disease process[3] despite the fact that over 90% is excreted within 24 hours.[4] The disease process—a cellular proliferation of the lungs—develops remorselessly and seems to represent a progressive chronic inflammation. Only paraquat does this. The pathogenesis of this lesion requires further study, and from work already published it is clear that the manufacturers of the herbicide are devoting considerable efforts to discovering more about its mode of action on the mammalian cell.

Meanwhile what sort of hazard does such a compound present? Repeated small doses have no effect on laboratory animals, and repeated exposure seems to have no effect on argicultural workers, except that local irritation may occur after prolonged contamination of the skin. Yet the accidental ingestion of a single small quantity can provoke a fatal disease within two to three weeks. The only case known so far in which ingestion did not result in death is one in which a man swallowed the contents of the home garden pack of Weedol, containing 2.8 g. of paraquat formulated as granules.[5] Clearly a few drops from a watering-can containing this weedkiller are not likely to be dangerous to the suburban gardener. Nevertheless, the concentrate as issued to farmers and market gardeners can be very dangerous in a way that may mislead doctors owing to the delay in the onset of its effects. In a recent case (unreported) a child drank from a Coca Cola bottle in which its parent had put some paraquat illicitly obtained from a market garden. The child appeared to recover from the acute effects, was sent home, but died two weeks later.

Many modern herbicides have a very low acute toxicity to man. The immediate effects of paraquat are mild, but fatal poisoning may be delayed in onset. In any case of suspected suicide or accidental poisoning from swallowing of a weed-

[1] Ministry of Agriculture, Fisheries, and Food. *Reports on Safety, Health, Welfare and Wages in Agriculture*, 1961-1965. H.M.S.O.
[2] Bullivant, C. M., *Brit. med. J.*, 1966, **1**, 1272.
[3] Clark, D. G., McElligott, T. F., and Hurst, E. W., *Brit. J. industr. Med.*, 1966, **23**, 126.
[4] Daniel, J. M., and Gage, J. C., ibid., 1966, **23**, 133.
[5] Unpublished information.

killer the doctor would be well advised to make certain that the preparation was not a dipyridyl type of herbicide before assuming that an early recovery from poisoning will be permanent. A sample of urine should be analysed as soon as possible, and if this shows that the patient has absorbed any significant amount of paraquat he should be treated, in the absence of any known specific measures, on general principles. These would include stomach wash-out and the promotion of diuresis by mannitol. If there are signs of renal failure, dialysis should be considered. Unfortunately no treatment has yet been found effective once the lung lesions develop.

Allergic Alveolitis

Mushroom-worker's lung, like bird-fancier's lung,[1] is one of a group of pulmonary allergic diseases due to inhaled organic dusts, for which the term "extrinsic allergic alveolitis" has been suggested. Farmer's lung is the classical example.

The inhalation of organic dusts may cause two main forms of allergic disease, affecting either the bronchi, with the production of asthma, or the peripheral lung tissues, with the production of a mainly alveolar reaction. An analysis[2] of the factors which determine these important differences shows that atopic persons give bronchial asthmatic reactions which are mediated by non-precipitating, reaginic antibody (type I allergy[3]), whereas non-atopic persons give predominantly alveolar reactions, provided the dust particles are small enough to penetrate to the alveoli. These reactions are mediated by precipitating antibody (type III allergy[3]).

Many organic dusts cause allergic alveolitis. The diseases include farmer's lung,[4] bagassosis,[5] maple-bark disease due to the fungus *Cryptostroma corticale*,[6] lung disease due to the grain weevil *Sitophilus granarius*,[7] bird-fancier's lung due to avian antigens,[8] and pituitary snuff-taker's lung due to porcine and bovine posterior pituitary powder.[9] In the *B.M.J.* this week (page 708) Dr. Alex Sakula adds another—namely, mushroom-worker's lung, due to actinomycetes that flourish in hot, damp vegetable matter. In all of these diseases precipitins have been found in the serum against the relevant antigens. Other similar diseases in which precipitins have either not yet been found or not certainly identified include suberosis due to cork dust, paprika-splitter's lung, smallpox-handler's lung,[10] and the chronic lung disease of New Guinea natives attributed to dust from thatched roofs.[11]

Extrinsic allergic alveolitis, whatever its cause, has a common pattern of clinical symptoms, all of them present in the patients suffering from mushroom-worker's lung. They are entirely different from the wheezing of the asthmatic patient, in whom pulmonary function tests show airways obstruction. Systemic reactions are an important feature of allergic alveolitis, and may consist of fever, chills, and malaise, with aches and pains, followed by a marked loss of weight. The pulmonary symptoms and signs are those of a chiefly alveolar reaction. They consist of cough, and of dyspnoea, which is often severe and out of proportion to the paucity of the crepitant rales which may be heard. Tests of pulmonary function show a restrictive defect, with impairment of gas transfer and decrease in lung compliance, with little, if any, evidence of airways obstruction.[4 12 13] Such tests are now becoming an essential part of the investigation of patients with lung disease.

Radiographic examination in the early stages usually shows nodular shadows, frequently micronodular, and of a wide distribution, as might be expected from the inhalation of large amounts of finely particulate dust capable of reaching the alveoli. In the late stages there is radiographic evidence suggestive of fibrosis, with diffuse honeycomb changes, affecting particularly the upper lobes.

Histological examination of the lungs shows, in the early stages, infiltration of the alveolar walls with polymorphonuclear, lymphoid, and plasma cells, and in the later stages epithelioid-cell granulomata and fibrosis are present. In about one-quarter of patients with farmer's lung bronchiolitis obliterans was also found.[14]

The disease may present in two ways.[4 8] The classical form consists of systemic and pulmonary symptoms appearing five to six hours or more after exposure to the dust. Such attacks may subside rapidly, only to recur on re-exposure. The disease may also have an insidious onset and is then, if anything, the more dangerous, because the relationship of the symptoms to the causal exposure is far less likely to be suspected. The gradual development of the disease results in the patient's seeking medical attention when fibrosis is far advanced and irreversible. The differences in the mode of onset appear to be related to the frequency and intensity of exposure to the dust. Inhalation tests in both groups of patients provoke the same classical attacks of the disease, coming on after five to six hours or so.[8]

Management of the disease must be based on avoidance of the antigens. This makes it imperative that inhaled dusts should be considered as possible causes in patients with disease affecting the alveoli or with pulmonary fibrosis. Fortunately, the precipitin test offers a means of identifying the antigen, though the presence of precipitins can be taken in the first place only as evidence of exposure to the antigens. Inhalation tests help to confirm the cause by reproducing the disease, and when a new dust is recognized such tests are needed to establish the clinical relevance of the immunological findings. Once the significance of the serological tests has been established, inhalation tests may reasonably be omitted. Farmers can avoid exposure to thermophilic actinomycetes by keeping down the moisture content of the hay.[15] Mushroom workers face greater difficulties, because in the making of their compost many actinomycete spores are inevitably produced.[16] Masks are of limited value, because of the very small size of the spores of the thermophilic actinomycetes—only about 1 μ in diameter.[17]

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[2] *Medical Research Council Annual Report, 1966–67*, 1967, p. 74. H.M.S.O.
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